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Current Opinion in Chemical Engineering

Process integration and control in continuous bioprocessing

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Biopharmaceutical industry is presently facing multiple economic, political and regulatory challenges. The adoption of continuous bioprocessing is expected to partly alleviate these. Over the years, many technology solutions have been developed for various biotech unit operations which were hitherto operated in batch fashion. The next challenge is to integrate all unit operations to create a fully continuous manufacturing system. In this article, we discuss recent developments in process integration and control under a proposed framework consisting of modular, adaptation and merger approaches of integration with a particular emphasis on developments that have occurred in the past five years (2013–2018).

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Current Opinion in Chemical Engineering 2018, **22**:18–25

This review comes from a themed issue on **Biotechnology and bioprocess engineering: biomanufacturing**

Edited by **Michael Betenbaugh** and **Nigel Titchener-Hooker**

https://doi.org/10.1016/j.coche.2018.08.005

Introduction

Modus operandi for biopharmaceutical industries has been batch processing, primarily because of small production volumes that were required, high value products, extensive use of off line analysis for estimation of product quality, and the large decision time that is available between moving from one process step to another [1••]. Moreover, in a market dominated by unique and patent-protected products, time-to-market is considered more desirable than process optimization, manufacturing efficiency, or production costs [2]. However, growing pressure from the government and the patients to lower costs of biotherapeutics as well as gradually increasing competition from biosimilars have pushed biopharmaceutical industries to explore continuous processing [2]. Key drivers include economics, consistent product quality, and regularity guidelines [3]. A number of continuous technologies, enlisted in Figure 1, have been developed for the various upstream and downstream unit operations [4•,5,6].

Continuous production requires the user to link all unit operations to create a single flow [3]. Therefore, process integration forms a critical component of continuous bioprocessing. Three approaches have been employed by the researchers for achieving process integration. In the first approach, called 'modular approach', each unit operation can be considered as a separate independent unit (called module), which can be optimized independently and is integrated with another module without any modification using some facilitator technology if required (such as use of surge vessels). In the second approach, called 'adaptation approach', one or both unit operations are adapted (or modified) in a manner that allows their seamless integration (such as modifying anion exchange resins to allow loading at higher salt concentrations has enabled integration to the preceding cation exchange chromatography) [7]. Finally, the third approach, called 'merger approach', consists of merging multiple unit operations into one single step (such as expanded bed adsorption combines clarification, initial purification and concentration of harvest) [8]. In this review, recent developments related to process integration in biopharmaceutical manufacturing are discussed under the proposed categories.

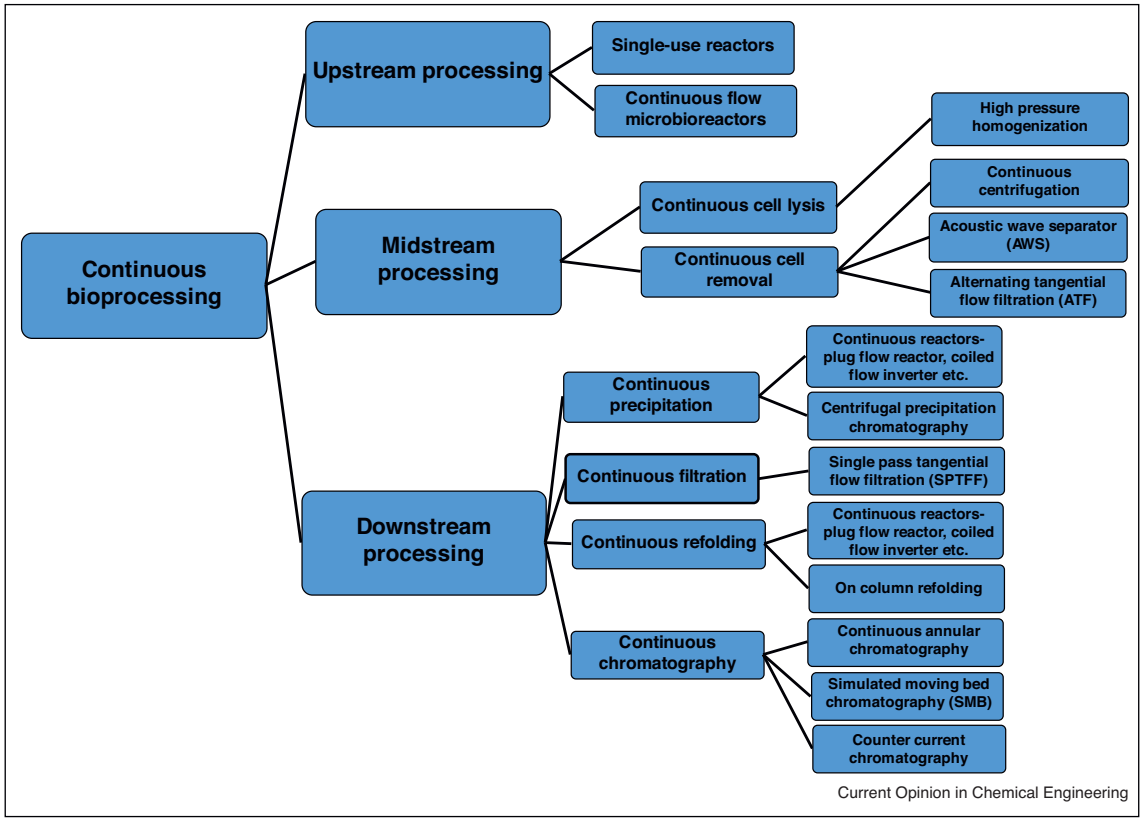
Modular approach

Modular approach subdivides a system into smaller parts called modules [9]. Each module is independently optimized and can be integrated via utilization of an enabler technology to facilitate their integration. A functional partitioning is maintained between different modules [9]. One can design a complex structure by employing independent modules. This approach of integration offers several advantages including reduction of optimization cost and ease of implementation. When two unit operations do not have an overlapping operating space, one needs to have facilitator technology for integration (Figure 3). These enabler technologies can also be regarded as modules. In subsequent sections, we describe some of these technologies.

Cell retention devices

For fully integrated biopharmaceutical manufacturing, continuous upstream and downstream operations must be coupled [10]. Retention devices (Figure 2**a** and **b**) like alternating tangential filtration (ATF) and Acoustic Wave

Figure 1



Schematic of the various continuous manufacturing technologies available for various stages of biopharmaceutical manufacturing.

Separators (AWS) are not only helpful in maintaining high cell concentration inside perfusion reactors but also provide clarified harvest which can be directly captured [1••,2,11]. Feasibility of long term operations connecting continuous cell culture with continuous capture step [2,12] and entire downstream process [13•,14] has been demonstrated by several researchers [2,12,13•,14].

Continuous buffer exchange/diafiltration

Diafiltration is used for the final formulation of essentially all biopharmaceuticals drug substance. It can also provide preconditioning of the feed stream before other purification steps in the downstream process and small molecule contaminant removal. Continuous diafiltration is carried out by multistage arrangement of membranes such that retentate from preceding stage becomes feed for the following stage [15]. Diluent is added to this multistage arrangement in a cocurrent or countercurrent manner (Figure 2**d**,**e**). More recently, single pass inline diafiltration (ILD) module has been proposed and it can be operated in a continuous manner to deliver benefits including lower shear exposure, reduced minimum working volume and elimination of foaming/mixing concerns [16]. This approach has been demonstrated to deliver step recovery of >99.75% [17].

Single pass tangential flow filtration (SPTFF)

SPTFF (Figure 2**c**) offers a solution for achieving continuous inline concentration [18]. Commercial solutions that are available presently include use of specially designed diverter plates that allow any existing TFF cassettes to be configured in SPTFF within a single holder [19]. This approach offers flexibility of configuring SPTFF from existing membranes. An alternate approach involves use of SPTFF as inline concentrator modules which are holderless and utilize a staged flow path design and a built-in restrictor to achieve concentration factors suitable for inline volume reduction applications [20]. Researchers have demonstrated use of SPTFF in different parts of the manufacturing process - for concentrating cell culture harvest [19,21], chromatography elution pools [22] and final drug substance [23].

Surge vessels

Surge vessels play an important role in integration of unit operations, especially operations which function in semi-continuous and cyclic manner. One such unit operation is multicolumn operation which may have an intermittent and periodic output. This output can also have other gradients like pH, conductivity and concentration. Because of discontinuous output, one requires an